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EXPERIMENTAL ENDOCARDITIS

Barry Bruce Perlman

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EXPERIMENTAL ENDOCARDITIS

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To Lois, my wife, and my parents.

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GENERAL INTRODUCTION:

PRIOR TO THE ADVENT OF ANTI-MICROBIAL CHEMOTHERAPY THE MORTALITY RATE IN HOSPITALS FOR PATIENTS HAVING BACTERIAL ENDOCARDITIS APPROACHED 80% (1); THE ATTAINMENT OF THE "BACTERIA-FREE STAGE" RANGED FROM 0-3% (2,3). SUBSEQUENTLY, THE UTILIZATION OF APPROPRIATE THERAPY SUBSTANTIALLY REDUCED THE MORTALITY FIGURES (4,5). THE BELIEF THAT THE CONQUEST OF THIS FORMIDABLE DISEASE WAS AT HAND PROVED DELUSION. TODAY MORTALITY FIGURES REMAIN IN THE RANGE OF 17-35% (4-6). FURTHERMORE, WITH THE ADVENT OF CARDIAC SURGERY PROCEDURES INVOLVING THE PLACING OF VALVES AND OTHER PROSTHESES, THE INABILITY TO CHEMICALLY STERILIZE POST-OPERATION ENDOCARDITIS HAS BECOME A TAXING PROBLEM. FOR THIS GROUP MORTALITY RATES HAVE AGAIN CLIMBED TO THE 50-75% RANGE (7-12). ATTEMPTING TO ASSESS THE EFFICACY OF NEW MOLECULES TO COMBAT INFECTIOUS ENDOCARDITIS MAY BE FACILITATED BY THE METHODS TO BE DESCRIBED IN THIS THESIS.

THE STATISTICS REFERED TO IN THE PRECEDING PARAGRAPH WOULD, BY THEMSELVES, PROVIDE A RAISON D'ETRE FOR PURSUING THE STUDY OF THIS DISEASE. OFTEN, HOWEVER, IMPETUS AND INTEREST ARE DERIVED FROM OTHER THAN PROBLEMATICAL NUMERICAL EXPOSITION. OF THE VAST LITERATURE TREATING OF BACTERIAL ENDOCARDITIS, ONE ARTICLE STANDS ALONE FOR THE HUMANITY WITH WHICH IT APPROACHES THE TOPIC. ITS EMPHASIS IS NEITHER PATHOPHYSIOLOGIC NOR STATISTICAL, RATHER IT IS PSYCHOLOGIC. THE AUTHOR, SOMA WEISS (13), HAS PROVIDED A VEHICLE BY WHICH TO MOVE OUR SENSE OF EMPATHY. THE PUBLICATION CONSISTS OF THE DESCRIPTIVE, INTROSPECTIVE TRANSCRIPT OF A HARVARD MEDICAL STUDENT WHO, DURING HIS FOURTH YEAR, DEVELOPED SUBACUTE BACTERIAL ENDOCARDITIS AND RECORDED HIS REACTIONS AND FEELING TO THE DISEASE PROCESS HARBORED WITHIN HIM AND TO ITS TANGIBLE MANIFESTATIONS. THE PATIENT PROVIDES EXCELLENT DESCRIPTIONS OF HIS LIFE WITH RHEUMATIC HEART DISEASE, THE SENSATIONS AND IMPLICATIONS OF THE WATER-HAMMER PULSE WHICH ACCOMPANIED

his aortic insufficiency, the discomfort and subsequent pain following splenic infarction, and the sense of trepidation felt on first noticing the appearance of petechiae. With a past history of rheumatic heart disease and the development of antibiotics still beyond the horizon of history, the fellow's fate was sealed. The interaction of soma and psyche become clinically preeminent at this point in the natural history of the disease. "By this time I was quite reconciled to my fate, but nevertheless was continually seeking new treatment. I am entirely sincere when I say that I sought new treatment not in any serious endeavor to cure the disease or prolong my life, but simply to satisfy the urge that something was being done. The psychological factor was now of most importance, and if I were to lie in bed much longer, I needed the moral satisfaction of having something done to me, however useless it might be." It is rare that a sufferer from a disease becomes an articulate observer of his fate; his thoughts would be well heeded. This patient tells us that we must pursue the cure of the disease through our expanding knowledge of pathophysiology, but that when this provides us with no further alternatives at a given point in time, we must be flexible and able to switch our emphasis to the psychological support of the patient, rather than withdrawing from him. The scientific pursuit of the underpinnings of bacterial endocarditis and the search for means by which to cope with it have extended for almost one hundred years.

The literature dealing with the experimental approaches to bacterial endocarditis is an extensive one. That mechanical trauma to the heart valves provides a reliable method of predisposing them to bacterial endocarditis has long been known. Much of this early work was undertaken in the academies of Germany late in the Nineteenth and early in the Twentieth centuries. The first use of this technique is attributed to Rosenbach, 1878, (14), who by damaging the aortic cusps with a non-sterile

rod passed down the carotid artery established bacterial endocarditis in dogs and rabbits. A similar technique was later used by Wyssokowitch in 1886 (41). Others, such as Ribbert, 1885, (15), employed suspensions of bacteria along with various granular substances, such as starch from potato cultures, to inflict the desired valvular injury (16-18). No matter what the mode of injury, bacterial endocarditis followed the innoculation of bacteria. The sought after lesion could also be induced if the techniques of injury followed the implantation of microorganisms (19). Powers in 1929 (20) and later Harken in 1942 (21) obtained similar results by the placement of metal clips on the free margin of the posterior mitral leaflet; introduction was through the auricular appendage. In many respects this procedure is similar to today's prosthetic heart surgery. Consequently, it is easy to understand why those undergoing such procedures are at higher risk with respect to this disease; the state of increased risk is confirmed by statistics previously presented.

In addition to surgical procedures which predispose to aortic insufficiency (22-25), it was found that bacterial endocarditis could be induced by other techniques leading to severe hemodynamic changes in the experimental animal. The creation of fistulae (22, 26-29), as between aorta and inferior vena cava, has this result, as does the simulation of high altitude with and without hemodynamic stress and bacteremia (30-31). The induction of pressor episodes caused by the injection of pitressin was employed by Nedzel to stimulate the valvular changes necassary for subsequent bacterial localization and proliferation (32). Alteration of the lymphatic drainage of the heart too leads to a susceptible state (33). The induction of systemic immunologic reactions (34) and the injection of large numbers of organisms (35) have also proved profitable approaches. The manipulation of the endocrine environment too has been utilized (36).

Each of the modes mentioned thus far for the induction of bacterial

ENDOCARDITIS INFLICTS A SUBSTANTIAL DEGREE OF TRAUMA ON THE EXPERIMENTAL HOST. EACH IS CONTINGENT ON TECHNIQUES WHICH ALTERS THE NATURAL HISTORY OF THE DISEASE THEY PRODUCED BY MODULATING THE RESISTANCE TO INFECTION OF THE EXPERIMENTAL ANIMAL. IN CONTRADISTINCTION, GARRISON AND FREEDMAN (37) HAVE REPORTED A TECHNIQUE FOR ACHIEVING BACTERIAL ENDOCARDITIS WHICH IS RELATIVELY ATRAUMATIC TO THE EXPERIMENTAL RABBITS. FURTHER, THE POSSIBILITY EXISTS WITH THIS MODEL OF REMOVING THE INITIAL TRAUMATIZING AGENT, THUS LEAVING THE ANIMAL'S DEFENCES FREE TO TRY TO COMBAT THE THREATENING BACTERIA. BY INTRODUCING A CATHETER THROUGH THE FEMORAL VEIN AND PASSING IT INTO THE RIGHT AURICLE, IN PROPINQUITY TO THE TRICUSPID VALVE, STERILE MARANTIC AND VALVULAR ENDOCARDITIS COULD BE INDUCED; THE INTRODUCTION OF AS FEW AS 10^2 STAPHYLOCOCCI THROUGH THE CATHETER RESULTED IN BACTERIAL ENDOCARDITIS. THE ORIGINAL DECISION TO EMPLOY IMPLANTED POLYETHYLENE CATHETERS AS A SOURCE OF BACTERIA WAS A RAMIFICATION OF THE OBSERVATION THAT INDWELLING CATHETERS OFTEN SERVE AS NIDI OF INFECTION IN MAN (38-40).

THE TWO EXPERIMENTS WHICH COMPRISE THE BODY OF THIS THESIS UTILIZE AND EXTEND THE TECHNIQUES DEVELOPED BY GARRISON AND FREEDMAN SO AS TO FURTHER DEVELOP THIS ACCESSIBLE MODEL FOR THE STUDY OF BACTERIAL ENDOCARDITIS AND FURTHER PURSUE THE NATURAL HISTORY OF THE DISEASE. THE FIRST PART OF THE THESIS WILL DEMONSTRATE THE USE OF THE CATHETER IMPLANT TECHNIQUE FOR INDUCING STERILE AND BACTERIAL ENDOCARDITIS OF THE AORTIC VALVE. THE SECOND EXPERIMENTAL SECTION WILL TRACE THE NATURAL HISTORY OF THE ESTABLISHED DISEASE AFTER REMOVAL OF THE CATHETER .

Experimental section I: Staphylococcal infection of the aortic valve following placement of a polyethylene catheter in the left side of the heart.

Introduction to experiment I:

The introduction of polyethylene catheters into the right side of the heart has recently been shown to induce the formation of sterile marantic endocarditis (37). It was further noted that the inoculation of as few as 10^2 staphylococci through the catheter would regularly result in staphylococcal endocarditis. In these experiments the catheter remained in the right heart until the animal was sacrificed; it thus served as a possible source of mechanical trauma and as a nidus for the seeding of microorganisms.

The present study was undertaken to test wheter it was possible to establish sterile and infective endocarditis in the left side of the heart utilizing techniques which previously had been shown to be effective on the right side.

Materials and Methods:

The experimental animals were five pound, white New Zeland rabbits. The animals received 50-60 mgs of Sodium Pentobarbital intravenously and inhaled ether as anaesthesia. The cannula utilized was a sterile polyethylene catheter, ("Intramedic," Clat-Adams , PE90, radiopaque, I.D.:0.034", O.D.0.050").

The right carotid artery was ligated and incised, and the catheter inserted a distance of about 3½ inches until resistance was met. It was then withdrawn slightly, perhaps 1/16 to 1/8 of an inch, and tied in place. The tip thus remained in a position just above the semilunar cusps of the aortic valve. The catheter was then filled with the appropriate fluid and the free end bent over and tied upon itself. The catheter remained _in situ_ until the death or sacrifice of the animal. Skin incisions were closed

with silk over the free ends of the catheter. Although rigorous sterile techniques were not followed, local wound infection was not encountered.

The microorganisms were the Giorgio strain of coagulase positive *staphylococcus aureus* which had been used in this laboratory previously. The organisms were cultured overnight (10^8 colony forming units per ml) in trypticase soy broth and appropriate dilutions were administered through the catheter. Inocula were enumerated by counting viable bacterial units in serially diluted agar pour plates after a one day incubation period. The catheter held about 0.1 ml per inch. Of the diluted experimental culture 0.5 ml was injected to prevent blood clot formation at the tip of the catheter.

Two series of animals were studied.

Group I: rabbits with catheters containing sterile saline.

Group II: rabbits with catheters containing staphylococci.

Animals were killed by the intavenous injection of 120 mgs of Sodium Pentobarbital and ethyl ether inhalation if necessary. Post-mortem examinations were performed immediately following sacrifice of the rabbit or at such time as the animal was found dead. A terminal blood sample was drwn from the marginal ear vein or the inferior vena cava. Aseptic technique was rigorously observed during the post-mortem examination. The organs were examined grossly and pathological specimens taken. If the animal had not died the kidneys, liver, and spleen were homogenized *in toto* and cultured quantitatively. The spleens were weighed upon removal. One cc of the urine from the bladder was cultured. Viable bacterial units from samples cultured were counted after a 24 hour incubation period.

Special care was taken in examining the heart. The catheter was clamped on the arch of the aorta prior to the removal of the heart. The heart was then carefully examined to locate the tip of the catheter and to detect the location of vegetations. The contents of the catheter were

expressed and cultured. The vegetations were then incised and a small platinum loopful of material was recovered for Gram stain and culture. Where Gram stain did not reveal numerous bacteria, 2 or 3 sites of the vegetation were cultured. The loop employed carries about 0.001 ml of liquid.

Results:

Group I: This series of animals had catheters filled with sterile saline placed in their right carotid arteries. The catheters remained *in situ* until the rabbits were sacrificed or died, 18 to 42 days after operation. The catheter tips were found in the region of the aortic valve in 6 animals and were discovered to be endothelialized along the wall of the aorta in two rabbits (table I). Sterile vegetations were present at the aortic valve or on other immediately adjacent tissue surfaces in each of the 5 of 6 animals with catheters free in the vascular system (Fig I). Among this group only one animal was found dead, the remainder were sacrificed. The single animal that did die had Gram negative rods cultured from the catheter contents and from the aortic vegetation. Kidney infarctions were noted in 87.5% (7/8) of the rabbits (fig 2). The spleens were weighed upon removal; splenic enlargement ($>$ 2 gms) was not noted. No microorganisms were cultured from the heart vegetations, catheter contents, organ homogenates, blood, or urine samples.

Group II: The nine rabbits of this group were cannulated with catheters filled with 10^4-10^6 staphylococci. At post-mortem examination, 7 of the rabbits had vegetations from which staphylococci were cultured (Fig 3). One animal had vegetations which when cultured grew staphylococci and gram negative organisms as well. The catheter was not recovered from the heart of the remaining animal; it was probably short and not in the proper position (table 2).

In the 8 infected rabbits, the catheter tips were in propinquity to

the aortic valve. The vegetations were located predominantly on the aortic cusps, but were also found on a papillary muscle, the mitral valve, and on other surfaces contiguous with the aortic valve. Evidence of infarction or abcessof the kidneys was present in 78% (7/9) of the animals. Splenic enlargement (>2 gms) was evident in 50% (3/6) of the rabbits whose spleens were weighed. Only three rabbits of this series had terminal blood cultures taken; two were positive. Of these rabbits 89% (8/9) died within the first 18 postoperative days; the single surviving animal was sacrificed on day 32; the catheter was not recovered from this rabbit and endocarditis was not found.

The gross appearance of the vegetations on the aortic valves was similar to those found in human endocarditis and to those described in previous work on the right side of the heart using this model (37). The lesions were 1-5 mm, friable, aciniform, pale-pink excrescences in the infected rabbits. The lesions in the animals with sterile endocarditis were less friable, flatter, and pale. They distorted the valves to a lesser degree. Lesions occurred in similar positions in both series.

Histological differences existed in the lesions of the animals inoculated with bacteria and those into which sterile saline was injected. Rabbit 181b was one into which a catheter containing sterile saline was placed. The microscopic examinationof the lesions revealed bland vegetations consisting of fibrinand rare white cells. Rabbit no. 245 had large masses of bacteria situated amongst platelets and fibrin; mononuclear cells and fibroblast infiltration were evident. Polymorphonuclear leukocytes occurred only rarely in the vicinity of the bacteria. Areas of myocardial necrosis, containing zones of calcification, were noted. Renal lesions were typical of anemic infarcts or abcesses. No glomerulonephritis was observed.

EXPERIMENTAL SECTION II: NATURAL HISTORY OF CATHETER INDUCED STAPHYLOCOCCAL ENDOCARDITIS FOLLOWING CATHETER REMOVAL.

INTRODUCTION TO EXPERIMENT II:

TECHNIQUES HAVE BEEN DESCRIBED, IN A PREVIOUS PUBLICATION AND THE FIRST EXPERIMENTAL SECTION OF THIS THESIS, WHICH ALLOW THE REGULAR PRODUCTION OF STERILE OR BACTERIAL ENDOCARDITIS ON EITHER SIDE OF THE HEART (37). THE METHOD INVOLVES PASSING A STERILE POLYETHYLENE CATHETER, FROM THE PERIPHERAL VASCULAR SYSTEM, INTO EITHER THE LEFT OR RIGHT SIDE OF THE HEART. THE LESIONS INVOLVED THE TRICUSPID AND AORTIC VALVES PREDOMINANTLY. IF STERILE SALINE WAS INTRODUCED THROUGH THE CATHETER STERILE MARANTIC ENDOCARDITIS OCCURRED, WHEREAS THE INOCULATION OF STAPHYLOCOCCI RESULTED IN STAPHYLOCOCCAL ENDOCARDITIS. THE STUDIES TO THIS POINT HAVE DESCRIBED THE COURSE OF INFECTION WITH THE CATHETER IN PLACE.

THE WORK PRESENTED IN THIS EXPERIMENTAL SECTION WAS UNDERTAKEN TO LEARN OF THE NATURAL HISTORY OF BACTERIAL ENDOCARDITIS, ONCE ESTABLISHED IN THE MANNER PREVIOUSLY REPORTED, WHEN THE CATHETER WAS REMOVED.

MATERIALS AND METHODS:

THE MATERIALS AND METHODS FOR THE PRODUCTION OF RIGHT AND LEFT SIDED BACTERIAL ENDOCARDITIS HAVE BEEN DESCRIBED IN DETAIL IN A PREVIOUS PUBLICATION AND PART ONE OF THIS THESIS (37). IN BRIEF, POLYETHYLENE CATHETERS WERE INSERTED INTO THE HEART VIA THE PERIPHERAL VASCULAR SYSTEM. TO REACH THE REGION OF THE TRICUSPID VALVE, THE LEFT FEMORAL VEIN WAS EXPOSED AND A CATHETER PASSED INTO IT FOR A DISTANCE OF ABOUT 11-11½ INCHES. ON THE LEFT SIDE, A CATHETER WAS INSERTED, THROUGH AN INCISION IN THE RIGHT CAROTID ARTERY, FROM A DISTANCE OF ABOUT 3½ INCHES, SUCH THAT ITS TIP REMAINED IN PROPINQUITY TO THE CUSPS OF THE AORTIC VALVE. STAPHYLOCOCCI WERE INOCULATED THROUGH THE CATHETER TO PRODUCE INFECTIOUS ENDOCARDITIS.

AT VARYING INTERVALS THE ANIMALS WERE REANAESTHETIZED AND THE WOUND CREATED FOR CATHETER INTRODUCTION WAS REOPENED. THE DISTAL ENDOF THE

catheter was located and the catheter withdrawn. The carotid artery, proximal to the incision, was ligated with silk; the femoral vein was not tied. The skin wound was then tied with silk. Rigorous sterile technique was not followed and no wound infections were encountered. The contents of the catheters were expressed and quantitatively cultured. Because the catheters were not _in situ_ at autopsy, their placement was verified in early trials by x-ray. Proper placement of the catheter in the heart ususally resulted in transmission of pulsations along the fluid column in the catheter. The catheter placement proceures took 20-30 minutes; catheter removal took 5-10 minutes.

The microorganisms, a strain of staphylococcus aureus, used in these experiments were the same as those previously used in work with this model of bacterial endocarditis by this laboratory. The methods of preparation and introduction of the staphylococci have been described in a previous paper and part one of this thesis (37).

The animals were divided into two experimental groups.

Group I: rabbits with catheters containing staphylococci placed near the tricuspid valve.

Group II: rabbits with catheters containing staphylococci placed near the aortic valve.

A description of the procedure for post-mortem examination of the experimental animals following death or sacrifice has been described in a previous publication and in the previous experimental section of this thesis (37). The kidneys, spleen, and liver were grossly inspected and quantitatively cultured along with samples of urine and blood. The spleen was weighed.

As related in the earlier paper (37) and the first section of this presentation,special attention was given the examination of the heart. The heart was opened in order to locate vegetations. The vegetations were then

incised and a small platinum loopful of the material recovered for gram stain and culture. The loop used holds approximately 0.001 ml of liquid; therefore 0 colonies indicates less than 1000 viable units per gram. Where gram stain did not demonstrate numerous bacteria, 2 or 3 sites of the vegetations were cultured.

Results:

Group I: These rabbits had catheters containing staphylococci placed in the region of their tricuspid valves. The catheters were withdrawn from the animals several days prior to sacrifice. This series consisted of 18 rabbits. At post-mortem examination, 15 animals had sterile vegetations, and 3 rabbits had vegetations from which staphylococci were cultured (fig 4). The numbers of viable bacterial units recovered from the vegetations ranged from 3 to 41 colonies per 0.001 ml loopful. Vegetations occurred on the cusps of the tricuspid valve, the papillary muscles, and on the adjacent tissue surfaces in the atria and ventricles. Their size bore no relation to the findings of organisms. Grossly, they varied from large, friable, grayish masses to small, flat firm, pale excrescences (tables 3 & 4).

None of the animals with infected vegetations had evidence of splenic enlargement (> 2 gms); two rabbits with sterile vegetations did have splenomegaly. The cultures of the organ homogenates and other samples taken were only sporadically positive. When positive they grew only very small numbers of organisms. Positive terminal blood cultures were present in only 2 rabbits, 1 with septic and 1 with sterile vegetations; in each case the numbers of colonies was small, 4 and 9. The catheters which were removed usually were found to contain 10 colonies of staphylococci per ml.

The catheters were left *in situ* for from 2 to 14 days. The animals were sacrificed at from 3 to 6 days after the catheter was withdrawn.

The distribution of animals across these time ranges is shown in figure 5. Bacteriological studies, therefore, were carried out at from 5 to 19 days following the initial procedure. None of the rabbits died.

Group II: These rabbits had catheters containing staphylococci placed in proximity to their aortic valves; the catheters were withdrwn 3-6 days after placement. Of 14 rabbits, 6 had vegetations from which staphylococci were recovered and 8 had sterile vegetations (fig 6). The numbers of viable bacterial units cultured from these vegetations ranged from 63 to 1000 colonies per 0.001 ml loopful of material. The vegetations were most often found on the cusps of the aortic valve and on the wall of the aorta above and the ventricular surface below. Grossly, they varied from large friable masses, most often in rabbits having septic vegetations, to small firm, endothelialized excrescences confined to a single cusp (tables 5 & 6).

Splenic enlargement (> 2 gms) was noted in 3 of 6 rabbits with infected vegetations, whereas it was found in but 1 rabbit with sterile vegetations. Cultures of the organ homogenates of 3 of the animals with septic vegetations yielded only one set of positive cultures. Terminal blood cultures of 3 rabbits with infected vegetations yielded one positive result. Kidney infarcts or abcesses occurred with equal proportions in rabbits with infected and sterile vegetations; they were noted in 3 of 6 rabbits with septic vegetations and 4 of 8 with sterile vegetations.

In the animals which were found to have infected vegetations, the catheter remained in position from 3 to 5 days and the animals were sacrificed or died from 2 to 10 days after catheter removal; the total experimental time ranged from 5 to 13 days. The animals with sterile vegetations had catheters in position from 3 to 6 days and were sacrificed at times from 2 to 14 days after catheter withdrwl; the elapsed time from catherization to post-mortem examination was from 7 to 17 days.

THE DISTRIBUTION OF NUMBERS OF RABBITS WITHIN THESE TIME INTERVALS MAY BE ASCERTAINED FROM FIGURE 5. HALF OF THE RABBITS WITH INFECTED VEGETATIONS DIED; NONE OF THE RABBITS WITH STERILE VEGETATIONS DIED.

DISCUSSION:

A MODEL HAS BEEN DEVELOPED FOR THE PRODUCTION OF STERILE MARANTIC ENDOCARDITIS AND BACTERIAL ENDOCARDITIS ON THE LEFT SIDE OF THE HEART IN RABBITS. THE TECHNIQUE EMPLOYED WAS THAT WHICH HAD PREVIOUSLY BEEN SHOWN TO INDUCE RIGHT SIDED ENDOCARDITIS (37).

AS ANTICIPATED FROM EARLIER STUDIES, STERILE VERRUCOUS LESIONS WERE MANIFEST WHEN STERILE SALINE WAS INJECTED, WHEREAS STAPHYLOCOCCAL ENDOCARDITIS DEVELOPED WHEN STAPHYLOCOCCI WERE INOCULATED. IT IS INTERESTING TO NOTE THE GREAT DIFFERENCE IN SEVERITY BETWEEN THE BACTERIAL AND STERILE DISEASES. OF THE ANIMALS RECEIVING STERILE SALINE, 7 OF THE 8 RABBITS WERE SACRIFICED AND ALL WERE ALIVE FOR AT LEAST 18 POST-OPERATIVE DAYS. CONVERSELY, OF THE 8 RABBITS WITH LEFT SIDED INFECTIVE ENDOCARDITIS, ALL DIED BY THE EIGHTEENTH POST-OPERATIVE DAY. THUS THE BACTERIAL DISEASE WAS OF GREATER SEVERITY, DESPITE THE FACT THAT EMBOLI TO THE KIDNEYS OCCURRED IN ABOUT EQUAL PROPORTIONS IN THE TWO EXPERIMENTS.

IT IS REMARKABLE THAT THE LEFT SIDED ENDOCARDITIS CAUSED DEATH OF THE RABBITS, WHEREAS RIGHT SIDED INFECTIOUS ENDOCARDITIS RARELY RESULTED IN DEATH. THE RABBITS OF EXPERIMENT I GROUP II, IN THE PRESENT STUDY, HAD CATHETERS FILLED WITH STAPHYLOCOCCI PLACED IN PROXIMITY TO THEIR AORTIC VALVES. THE RABBITS OF THE PREVIOUSLY REPORTED STUDY HAD STAPHYLOCOCCI FILLED CATHETERS PLACED IN PROPINQUITY TO THEIR TRICUSPID VALVES THROUGH FEMORAL VEIN CATHERIZATION (37). THE RABBITS FROM THE PREVIOUS STUDY WERE SACRIFICED AT INTERVALS OF 8-41 DAYS; OF THE THIRTEEN ANIMALS IN THE STUDY, 8 SURVIVED BEYOND 18 DAYS. OF THE 8 ANIMALS OF THE PRESENT STUDY WITH INFECTED AORTIC ENDOCARDITIS IN WHICH THE CATHETER REMAINED _IN SITU_, ALL DIED DURING THE EIGHTEEN DAYS FOLLOWING OPERATION. OBVIOUSLY, THE COURSE OF THE DISEASE IN THE LEFT HEART WAS MORE FULMINANT THAN THAT IN THE RIGHT HEART. SYSTEMIC DISEMINATION OF THE STAPHYLOCOCCI, AS MEASURED BY THE POSITIVE CULTURES FROM ORGAN HOMOGENATES, WAS PRESENT IN THE MAJORITY OF RABBITS IN BOTH SERIES. THAT SYSTEMIC MANIFESTATIONS OCCURRED AS FREQUENTLY WITH RIGHT SIDED

as with left sided endocarditis contraoicts the usually accepted idea that the lungs serve as filters able to trap microorganisms in their course through the pulmonary circulation. It may be that these "paradoxical" septic emboli are able to reach the systemic circulation by traversing the lungs only after an initial barrage of microemboli alters lung tissue defences by causing microinfarcts or otherwise breaching the filter mechanism.

There is no obvious explanation for the fatal outcome of the left sided as compared with the right sided staphylococcal endocarditis in rabbits. The possibility exists that cerebral emboli result from left sided lesions, but this explanation would seem unlikely since sterile left sided endocarditis results in the same frequency of renal emboli and, therefore, would be expected to produce the same frequency of cerebral emboli; yet, sterile aortic endocarditis did not kill the rabbits.

Another possible explanation for the death of animals with left sided infective endocarditis is that lesions of myocarditis were seen which were not found in animals with right sided disease. It is not clear, howver, whether these lesions are peculiar to aortic valve disease or whether they may be a result of more extensive bacterial multiplication leading to more severe bacteremia in aortic disease. Unfortunately, the bacteriological studies carried out so far were not sufficiently detailed to permit comparison of the extent of infection in the two models. The data do show that at least 10^6 staphylococci / gm were present in the vegetations in both studies. However, the aortic animals were all dead for some time before examination. Careful culture of the entire vegetation would be required to make more accurate comparisons.

In previous experiments it was determined that as long as catheters containing staphylococci remained in the heart infected vegeataions would be encountered at post-mortem examination (37 & experimental section I). The experiments presented in experimental section II elucidate the consequences

OF CATHETER REMOVAL ON THE NATURAL HISTORY OF THIS MODEL INFECTION. WHEN CATHETERS WERE REMOVED FROM THE RIGHT SIDE OF THE HEART, THE RABBITS SEEMED CAPABLE OF PROPTLY STERILIZING THE VEGETATIONS. IN THE FEW ANIMALS IN WHICH SEPTIC VEGETATIONS WERE DISCOVERED, THE NUMBER OF VIABLE BACTERIAL UNITS WITHIN THE VEGETATION WAS SMALL. IN CONTRAST, AFTER CATHETERS WERE WITHDRAWN FROM THE AORTIC REGION 43% (6/14) OF THE RABBITS DEMONSTRATED INFECTED VEGETATIONS CONTAINING LARGE NUMBERS OF VIABLE BACTERIAL UNITS. THE COMPARISON OF ANIMALS WITH LEFT AND RIGHT HEART CATHERIZATIONS SHOWS THAT THE GROUPS WERE GENERALLY COMPARABLE, IE., THE LENGTH OF CATHERIZATION AND THE ELAPSED INTERVAL FOLLOWING REMOVAL OF THE CATHETER WERE SIMILAR IN THE TWO GROUPS. IF ANYTHING, THE ANIMALS WITH RIGHT SIDED ENDOCARDITIS HAD THEIR CATHETERS IN PLACE LONGER AND WERE LOOKED AT AFTER A SHORTER INTERVAL FOLLOWING REMOVAL OF THE CATHETER AS COMPARED WITH THE ANIMALS WITH LEFT SIDED ENDOCARDITIS. THUS THE ANIMALS WITH RIGHT SIDED ENDOCARDITIS HAD A SOMEWHAT LONGER PERIOD IN WHICH TO ESTABLISH THEIR INFECTIONS AND WERE EXAMINED AT A TIME WHEN THE INFECTIONS WERE LESS LIKELY TO HAVE HEALED. DESPITE THIS EMPHASIS, AN ENHANCED ABILITY TO EFFECTIVELY STERILIZE BACTERIAL ENDOCARDITIS IN THE RIGHT HEART AS CONTRASTED WITH THE LEFT HEART WAS APPARENT.

INDEED, ONCE THE CATHETERS WERE WITHDRAWN, SUGGESTION OF HEALING OF LESIONS APPEARED IN MANY OF THE ANIMALS WHICH HAD UNDERGONE RIGHT HEART CATHERIZATION; THE LESIONS WERE SMALLER AND FIRMER THAN THOSE PREVIOUSLY REPORTED IN WHICH CATHETERS REMAINED IN SITU UNTIL SACRIFICE (37 & EXPERIMENTAL SECTION I). THIS RESOLUTION WAS NOT EVIDENT AS OFTEN IN ANIMALS WHOSE LEFT HEARTS HAD CONTAINED CATHETERS. DEATH OF THE RABBITS WAS EXCLUSIVELY ENCOUNTERED IN ANIMALS WITH INFECTED AORTIC VEGETATIONS, AND NOT FOUND AT ALL IN ANIMALS WHICH HAD UNDERGONE RIGHT SIDED CATHERIZATION, IN THE CATHETER REMOVAL EXPERIMENTS.

IT MIGHT HAVE BEEN EXPECTED THAT A CRITICAL TIME WOULD HAVE EMERGED BEYOND WHICH, IF THE CATHETER REMAINED IN SITU AND WERE SUBSEQUENTLY REMOVED,

a self-sustaining disease would be induced. No such specific duration for right heart catherization became apparent. Even animals from which catheters were removed after two weeks were able to sterilize the vegetations. Although a critical time can not be defined in animals subjected to left heart catherization, an irreversible point may be established after after as few as 3 days of catheter implantation in some animals.

It is noteworthy that with only 2-3 days of cannulation, even in the absence of continuing infectious disease, gross sterile vegetations were already extant and were evident as long as 14 days later. The rapidity with which sterile lesions were established was equally evident on both sides of the heart.

The ability of the animals to effectively sterilize right sided bacterial endocarditis has its analogue in clinical medicine. It is known that a relatively small proportion of cases of bacterial endocarditis involves exclusively the right heart (42-45). Indeed, less than 2 % of cases are believed to involve the tricuspid valve alone (45-47). The disparity is to a large extent laid to the greater frequency of pre-existing valvular disease in the left heart. The emphasis on pre-existing lesions may require a redirection of attention in view of the results of this study. Even when damage, inducing susceptibility to endocarditis, is equal on both sides of the heart, as in the present study, infection on the right side was not maintained. Those factors responsible for the different course of infection in the right and left sides of the heart are not known. The difference in physical and metabolic environment may be important in explaining the different distribution of infectious valvular disease in man as it has been evoked to explain the distribution of non-infectious endocarditis (48).

Summary:

A model has been developed for the production of endocarditis of the aortic valve in rabbits. The technique is similar to that previously employed for producing right heart endocarditis; it depends on the catherization of the heart through the peripheral vascular system with a polyethylene catheter. The placement of sterile catheters results in sterile endocarditis. The introduction of staphylococci through the catheter results in infective endocarditis.

Sterile left sided endocarditis is well tolerated, whereas bacterial endocarditis on the left side of the heart regularly causes death of the animals. This contrasts with the rarity of death due to right heart infective endocarditis reported previously.

A previous study and experimental section I of this thesis described a technique for the induction of bacterial endocarditis in rabbits depending on the presence of a catheter, containing staphylococci, in either the left or right side of the heart. Part II was undertaken to follow the natural history of these infections after removal of the catheter. Following removal of the catheter, the rabbits with right heart endocarditis were able to sterilize their vegetations more effectively than animals with left heart endocarditis. Out of 18 rabbits with right sided endocarditis 3 had bacteria recovered, in low numbers, from the vegetations, whereas, 6 out of 14 animals with aortic endocarditis had large numbers of bacteria recovered.

Thus even when the conditions for establishing bacterial endocarditis are the same on both sides of the heart, infections heal more rapidly on the right side than on the left side.

TABLES AND FIGURES

TABLE I

GROUP I: LEFT HEART CATHERIZATION WITH CATHETER CONTAINING STERILE SALINE

RABBIT NO.	DAYS FOLLOWED	ANIMAL DIED	SACRIFICED	SPLEEN WT. (GMS)	STAPHYLOCOCCI RECOVERED*				GROSS FINDINGS
					CATH CONTENTS	BLOOD	ORGAN	VEGETATION	
96	24		X	1.39	NEG	NEG	KIDS- NEG URINE- NEG	NEG	CATH TIP AT AORTIC VALVE WITH VEG. KIDNEY INFARCTS BILAT.
101	18		X	1.27	NEG	NEG	KIDS- NEG URINE- NEG	NEG	CATH AT CUSPS; VALVE SWOLLEN. STERILE KIDNEY INFARCTS BILAT.
105	18		X	1.45	NEG	NEG	KIDS- NEG URINE- NEG	NEG	LARGE VEG ON CUSPS & SURFACE OF AORTA. LIVER: CHRONIC PASSIVE CONGESTION. SMALL KIDNEY INFARCTS BILAT.
135	48		X	1.54		NEG	KIDS- NEG URINE- NEG	NEG	CATH ENDOTHELIALIZED IN AORTA. VEG IN L. VENTRICLE & ON PAPILLARY MUSCLE. KIDNEYS NORMAL.
175	42		X	1.31	NEG	NEG	LIVER- NEG SPLEEN- NEG URINE- NEG	NEG	VEG IN AORTIC VALVE. SMALL INFARCT IN R. KIDNEY.
176	41		X	1.12			KIDS- NEG URINE- NEG	NEG	VEGS IN AORTIC ARCH & HEALED VEG IN VALVE. MULTIPLE HEALED KIDNEY INFARCTS.
181B	29	X		<2	CONTAM		KIDS- NEG SPLEEN- NEG	CONTAM	CATH TIP AT AORTIC VALVE. VEG AT AORTIC VALVE. OLD SCAR IN L. KIDNEY.
182	31		X	0.81	NEG		KIDS- NEG URINE- NEG	NEG	CATH ENDOTHELIALIZED IN AORTIC CUSPS. HEALED KIDNEY INFARCTS.

* VIABLE UNITS PER ML OR GRAM

TABLE 2

GROUP II: LEFT HEART CATHERIZATION WITH CATHETERS CONTAINING 10 - 10 STAPHYLOCOCCI

RABBIT NO.	DAYS FOLLOWED	ANIMAL DIED	SACRIFICED	SPLEEN WT. (GMS)	STAPHYLOCOCCI RECOVERED*				GROSS FINDINGS
					CATH CONTENTS	BLOOD	ORGANS**	VEGETATION	
92	4	X		<2		135		$>10^6$	CATH TIP AT AORTIC VALVE; CUSPS FILLED WITH VEG AND THROMBUS. KIDNEY INFARCTS BILAT.
155	13	X		3.39				$>10^6$	LARGE VEG REPLACING AORTIC VALVE; KIDNEY INFARCTS AND ABCESSES.
178	18	X						$>10^6$	LARGE AORTIC VEG; KIDNEY INFARCTS BILAT.
183	12	X						10^5 GRAM NEG RODS	SMALL VEG ON AORTIC CUSPS; L. VENTRICLE ENLARGED; NORMAL KIDNEYS.
184	32		X	1.26		NEG	KIDS- NEG URINE- NEG		NO VEG. CATH NOT LOCATED. KIDNEY INFARCTS BILAT.
220	1	X		1.66	$>10^6$			$>10^6$	FIBRINOUS VEG IN AORTIC VALVE.
245	3	X		4.1	$>10^6$			$>10^6$	CATH TIP AT AORTIC VALVE; VEGS ON AORTIC CUSPS AND MITRAL VALVE; SEPTUM MOTTLED. KIDNEY INFARCTS & ABCESSES BILAT.
252	5	X				20		$>10^6$	LARGE VEG IN AORTIC VALVE. KIDNEY INFARCTS BILAT.
270	3	X		3.98	$>10^6$			$>10^6$	VEG ON CUSPS OF AORTIC VALVE. SMALL KIDNEY INFARCTS.

* VIABLE UNITS PER ML OR GM.
** ORGANS NOT CULTURED WHEN ANIMAL FOUND DEAD.

TABLE 3

GROUP 1: RIGHT HEART CATHERIZATION WITH CATHETERS CONTAINING 10^4 - 10^6 STAPHYLOCOCCI

RABBIT NO.	DAYS CATH IN PLACE	TOTAL DAYS	SPLEEN WT. (GMS)	SACRIFICED	GROSS FINDINGS
ANIMALS WITH INFECTED VEGETATIONS:					
122	4	7	1.06	X	SMALL VEG NEAR TRICUSPID VALVE.
133	5	11	0.8	X	VEG ON R. ATRIAL WALL.
169	14	17	1.56	X	VEG ON TRICUSPID VALVE AND R. VENTRICULAR WALL.
ANIMALS WITH STERILE VEGETATIONS:					
110	5	8	2.91	X	QUESTIONABLE VEG.
114	5	9	1.79	X	QUESTIONABLE VEG ON TRICUSPID VALVE.
115	3	7	1.58	X	VEG ON TRICUSPID CUSPS AND ON R. ATRIAL WALL.
117	3	9	1.11	X	SMALL VEG ON R. ATRIAL WALL.
120	2	7	1.77	X	VEG ON R. ATRIAL WALL AND ON PAPILLARY MUSCLE.
124	6	10	1.65	X	FRIABLE VEG ON TRICUSPID VALVE AND WALL OF R. ATRIUM AND R. VENTRICLE.
125	6	10	1.90	X	LARGE VEG IN R. ATRIUM JUST ABOVE VALVE.
126	6	10	2.2	X	SMALL VEG IN R. ATRIUM.
129	5	11	1.07	X	VEG ON TRICUSPID VALVE AND WALL OF R. ATRIUM.
134	5	11	1.05	X	R. ATRIAL VEG.
143	14	18	1.2	X	VEG ON R. ATRIAL WALL.
144	13	19	1.12	X	SMALL ATRIAL VEG; SCARRING OF ONE TRICUSPID VALVE LEAFLET.
146	10	15	1.9	X	LARGE ATRIAL VEG.
158	7	10	0.71	X	SMALL ATRIAL VEG.
167	14	17	1.75	X	ATRIAL VEG.

TABLE 4.

GROUP I: RIGHT HEART CATHERIZATION WITH CATHETERS CONTAINING $10^4 - 10^6$ STAPHYLOCOCCI: BACTERIOLOGY

RABBIT	STAPHYLOCOCCI RECOVERED (VIABLE UNITS PER ML OR GM)							
NO.	CATH CONTENTS	R. KID.	L. KID.	LIVER	SPLEEN	BLOOD	URINE	VEGETATION
ANIMALS WITH INFECTED VEGETATIONS:								
122	$>10^6$	3	6	6	0	0	0	10×10^3
133	$>10^6$	0	1	0	0	18	10	41×10^3
169	$>10^6$	0	24	0	0	0	10	3×10^3; 7×10^3
ANIMALS WITH STERILE VEGETATIONS:								
110	$>10^6$	0	0	0	0	0	0	0
114	$>10^6$	0	0	0	0	0	0	0
115	$>10^6$	0	0	0	0	0	0	0
117	$>10^6$	0	0	0	0	0	0	0
120		0	0	10^3	0	0	<10	0
124	$>10^6$	0	0	0	0	8	<10	0
125	$>10^6$	10^3	10^3	0	0	0	<10	0
126	$>10^6$	10^3	0	10^4	10^3	0	0	0
129	$>10^6$	0	0	0	0	0	0	0
134	$>10^6$	0	0	0	0	0	0	0
143	$>10^6$	SAMPLES CONTAMINATED					0	0
144	$>10^6$	SAMPLES CONTAMINATED					0	0
146	$>10^6$	0	0	0	0	0	0	0
158	$>10^6$	SAMPLES CONTAMINATED					0	0
167	$>10^6$	0	0	0	0	0	0	0

TABLE 5.

GROUP II: LEFT HEART CATHERIZATION WITH CATHETERS CONTAINING $10^4 - 10^6$ STAPHYLOCOCCI

RABBIT NO.	DAYS CATH IN PLACE	TOTAL DAYS	SPLEEN WT. (GMS)	DIED	SACRIFICED	GROSS FINDINGS
ANIMALS WITH INFECTED VEGETATIONS:						
237	4	12	1.27		X	VEG AT BASE OF SEPTUM. KIDNEY INFARCTS BILAT.
238	3	5		X		L. VENTRICLE AND AORTIC CUSPS FILLED WITH VEG.
248	4	7	2	X		AORTIC VALVES FILLED WITH VEG. KIDNEY INFARCTS AND ABCESSES.
253	5	9	2.88	X		FRIABLE VEG FILLING AORTIC CUSPS. KIDNEY ABCESSES. LUNG INFARCT.
254	3	13	1.09		X	SMALL VEG ABOVE CUSPS OF AORTIC VALVE.
272	3	9	2.6		X	LARGE VEG. IN AORTIC CUSPS.
ANIMALS WITH STERILE VEGETATIONS:						
206	3	17	1.16		X	AORTA WRINKLED AROUND VALVES; NO VEG OR ENDOCARDITIS. OLD KIDNEY INFARCTS. HEMORRHAGIC LUNGS.
226	3	7	0.67		X	VEG ON LEFT SEPTUM. KIDNEY INFARCTS.
235	5	7	1.39		X	SMALL FRIABLE VEGS ON CUSPS AND WALL OF AORTA.
239	3	7	1.29		X	2 VEGS ON AORTIC WALL JUST ABOVE CUSPS.
244	4	10	2		X	VEG INSIDE AORTIC CUSPS. SMALL L. KIDNEY INFARCT.
249	4	10	1.8		X	ENDOTHELIALIZED VEG IN SINGLE AORTIC CUSP.
250	6	12	1.26		X	FRIABLE VEGS IN VALVE CUSPS; ENDOTHELIALIZED VEG IN CAROTID ARTERY.
256	3	13	2.47		X	AORTIC VEGETATION.

TABLE 6.

GROUP II: LEFT HEART CATHERIZATION WITH CATHETERS CONTAINING 10^4 - 10^6 STAPHYLOCOCCI: BACTERIOLOGY

RABBIT		STAPHYLOCOCCI RECOVERED (VIABLE UNITS PER ML OR GM)						
NO.	CATH CONTENTS	R. KID.	L. KID.	LIVER	SPLEEN	BLOOD	URINE	VEGETATION
ANIMALS WITH INFECTED VEGETATIONS:								
237	10^4	0	0	0	0	0	0	63×10^3
238								$>10^6$
248	$>10^6$							$>10^6$
253	$>10^6$							$>10^6$
254	$>10^6$							$>10^6$
272	$>10^6$	$>10^6$	$>10^6$	$>10^6$		54	<10	$>10^6$
ANIMALS WITH STERILE VEGETATIONS:								
206	$>10^6$	0	0	0	0	0	10	0
226	$>10^6$							0
235	$>10^6$							0
239	$>10^6$	0	0	0	0	0	0	0
244		0	0	0	0	0	0	0
249	$>10^6$	0	0	0	0	0	0	0
250	10^4	50×10^4	9×10^4	3×10^4	1×10^4	0	0	0
256		0	0	0	0	0	0	0

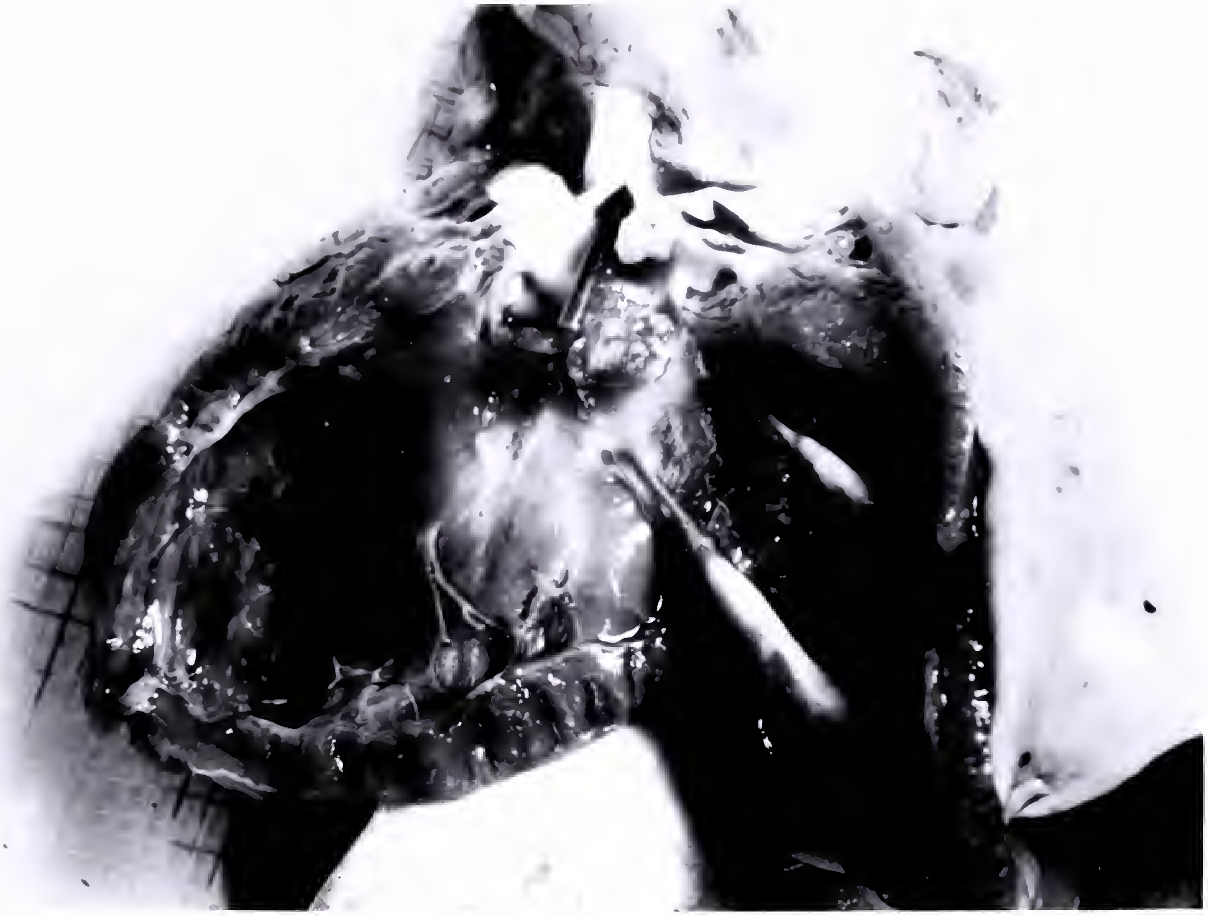

FIGURE 1:

RABBIT NO. 105. STERILE VEGETATIONS ON CUSPS AND SURFACE OF AORTA.

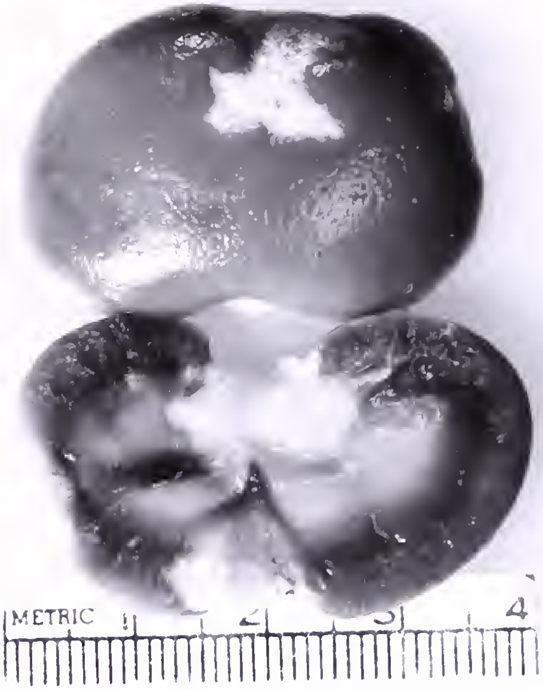

FIGURE 2:

RABBIT NO. 96. STERILE KIDNEY INFARCTS IN AN ANIMAL WITH STERILE AORTIC VEGETATIONS.

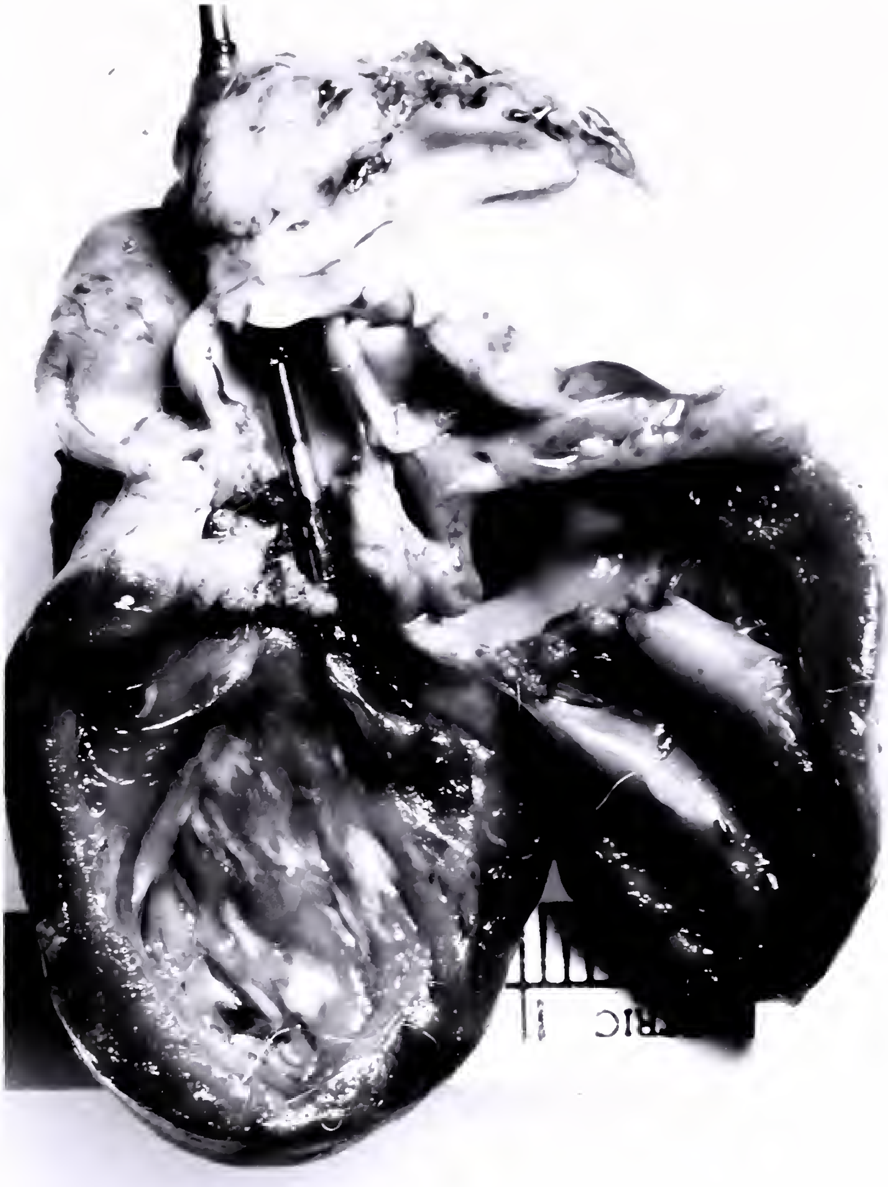

FIGURE 3:

RABBIT NO. 245. CATHETER TIP AT THE AORTIC VALVE. LARGE NUMBERS OF STAPHYLOCOCCI WERE CULTURED FROM THE VEGETATION. AREAS OF MYOCARDITIS ARE PRESENT.

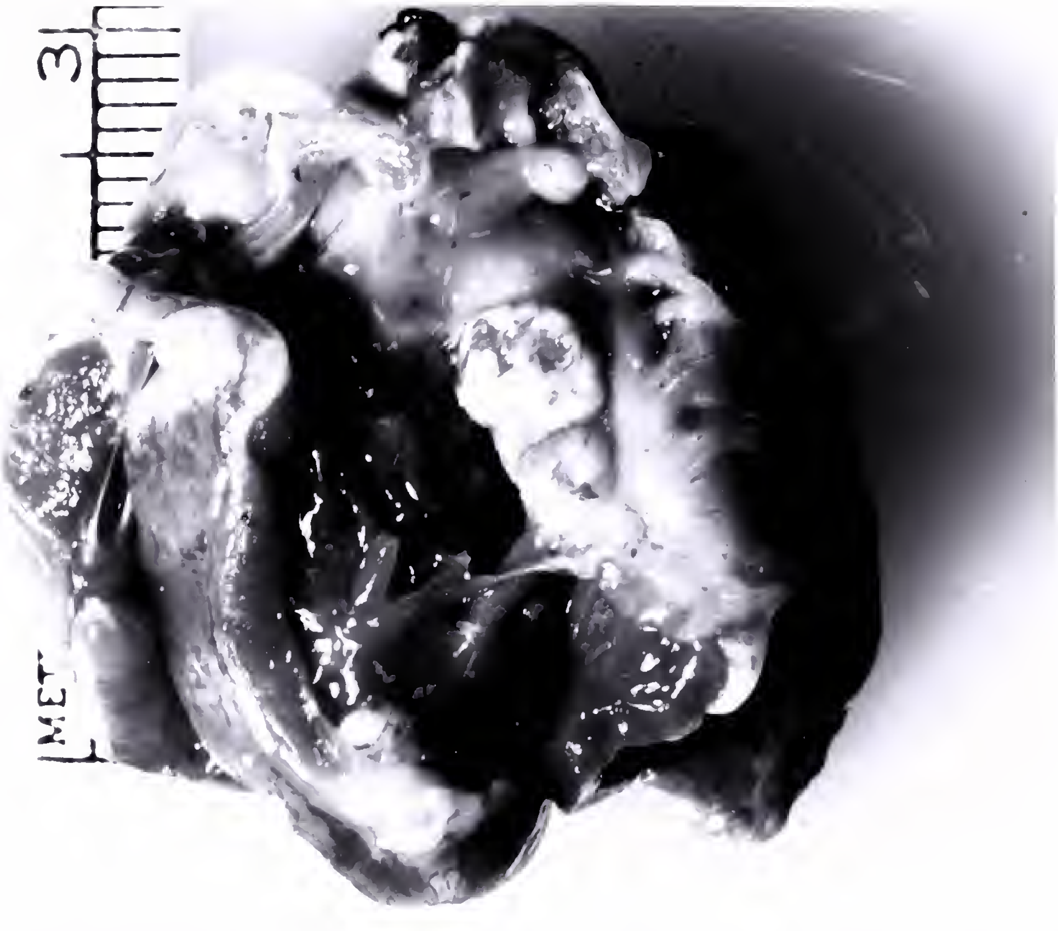

FIGURE 4:

RABBIT NO. 169. IFECTED VEGETATION ON TRICUSPID VALVE AND RIGHT VENTRICUALR WALL. SMALL NUMBERS OF ORGANISMS WERE RECOVERED FROM THE VEGETATION.

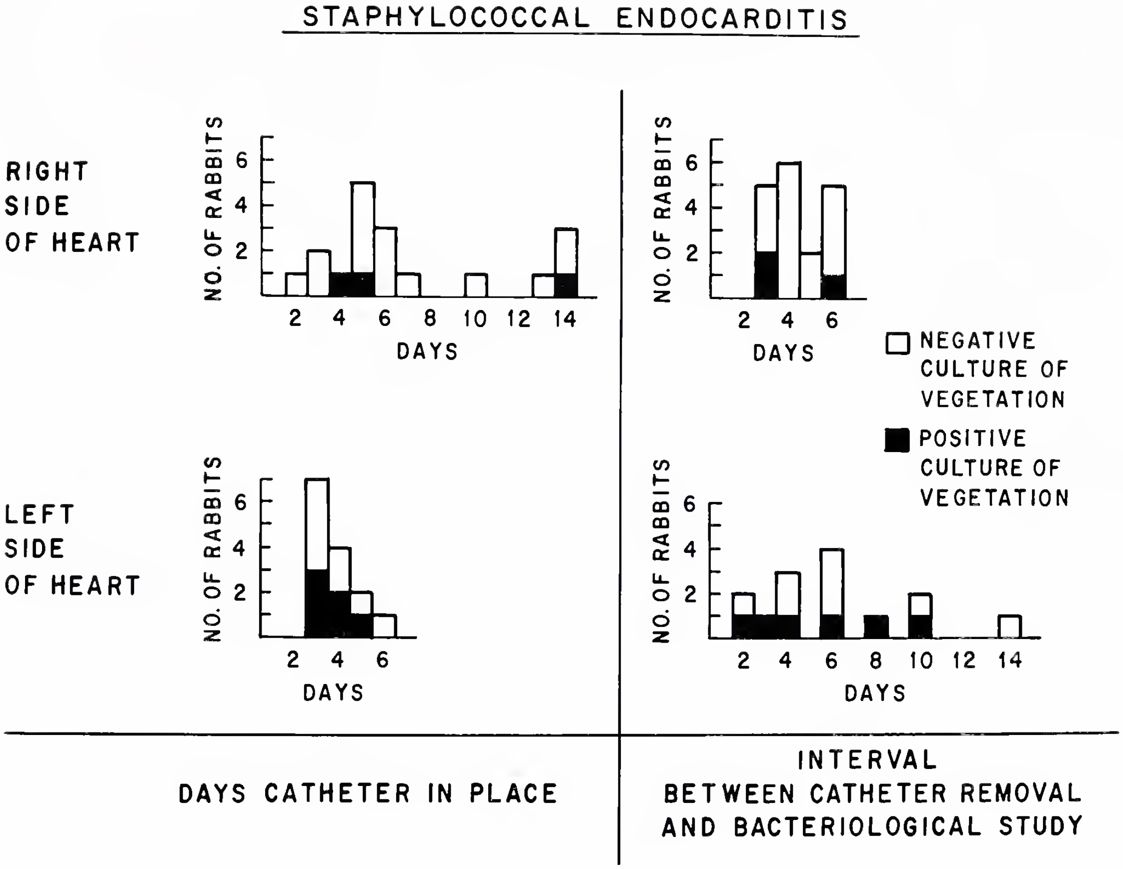

Figure 5:

Distribution of rabbits within intervals indicated.

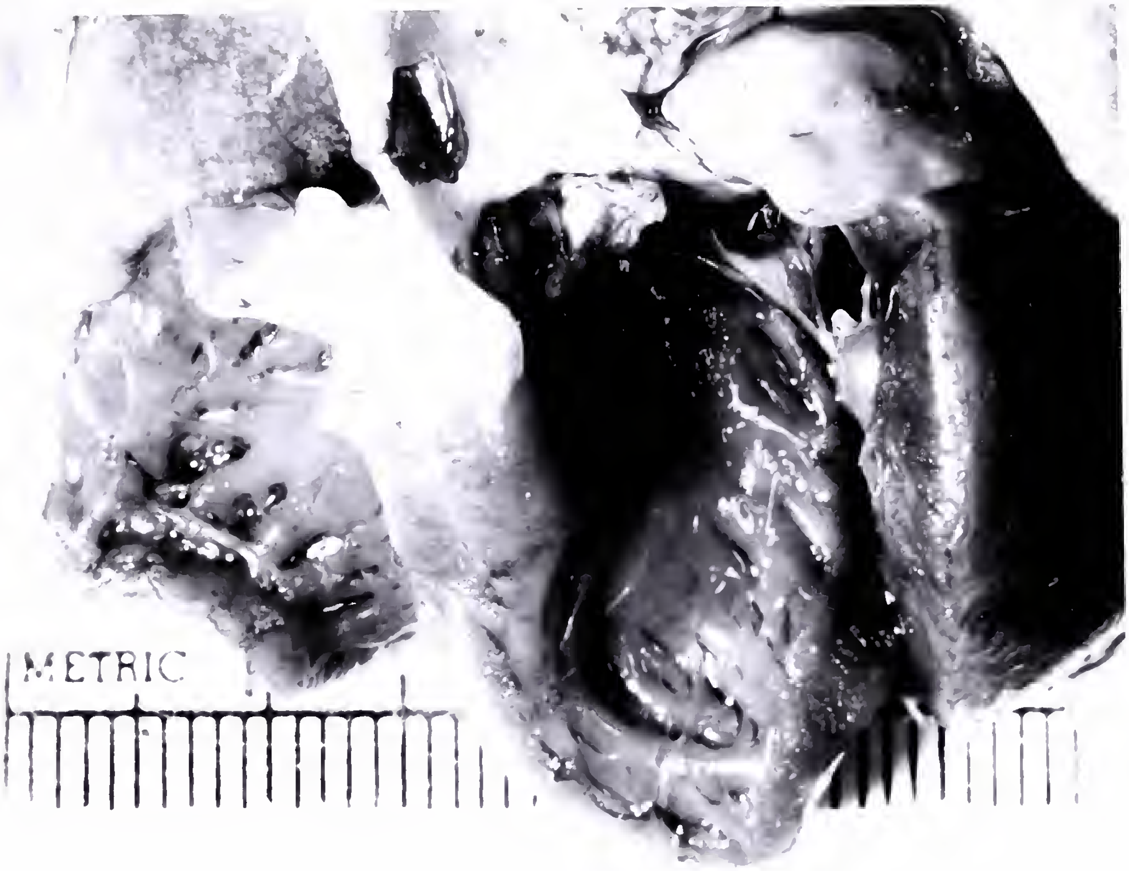

FIGURE 6:

RABBIT NO. 272. VEGETATIONS IN AORTIC CUSPS FROM WHICH LARGE NUMBERS OF STAPHYLOCOCCI WERE CULTURED.

Bibliography

1) Wilson, L.M., Etiology of bacterial endocarditis: before and since the introduction of antibiotics. Ann. Int. Med. 1963:58:946-952.

2) Libman, E. and Friedberg, C.K. Subacute Bacterial Endocarditis 2nd ed. (New York, Oxford, 1948).

3) Ichtmann, S.S., Treatment of subacute bacterial endocarditis: current results Ann. Int. Med. 1943:19, 787

4) Geraci, J.E. The antibiotic therapy of bacterial endocarditis. Med. Clin. N. Amer. 1958:42:1101-1140.

5) Vogler, W.R., Dorney, E.R., Bridges, H.A. Bacterial endocarditis: a review of 148 cases. Amer. J. of Med. 1962:32:910-921.

6) Friedberg, C.K., Goldman, H.M., Field, L.E. Study of bacterial endocarditis. Arch. Int. Med. 1961:107:6

7)Morgan,W.L., Bland,E.F. Bacterial endocarditis in the antibiotic era. Circulation 1955:19:753-765.

8)Bjork,V.O. Aortic valve replacement. Thorax 1964:19:369-378.

9) Killen, D.A., Collins, H.A., Koenig, G.M., Goodman, J.S. Prosthetic cardiac valves and bacterial endocarditis. Ann. Thoracic Surg. 1970:9:238-246.

10) Amoury,R.A., Bowman,F.O., Malm,J.R. Endocarditis associated with intracardiac prostheses. J. Thoracic and Cardiovasc. Surg. 1966:51:36-48.

11)Lord,J.W., Imparato,A.M., Hackel,A., Doyle,E.F. Endocarditis complicating open-heart surgery. Circulation 1961:23:489-497.

12) Braimbridge,M.V. Cardiac surgery and bacterial endocarditis. Lancet 1969: 1:1307-1309.

13) Weiss, S. Self-observations and psychologic reactions of medical student A.S.R. to the onset and symptoms of subacute bacterial endocarditis. J. Mt. Sinai Hospital 1941:8:1079-1094.

14) Rosenbach,O. Uber artificielle Herzklappenfehler, Arch. Exper. Path. u. Pharmakol. 1878:9:1 refered to by Koiwai,E.K., Nahas,H.C. Subacute bacterial endocarditis following cardiac surgery. A.M.A. Arch. Surg. 1956:73:272-8.

15) Ribbert,J. Beitrage zur Localisation der Infection skrankheiten. Deutsche med. Wchnschr. 1885:11:717 cited by Koiwai & Nahas (14).

16) Fulci,F. Experimentelle versuche uber die Existenz einer Endocarditis durch bakterielle Toxine. Beitr. Path. Anat. 1908:44:349 cited by Koiwai & Nahas (14).

17) Panichi,L., Guelfi,C., Beeinflussung des Endokards durch krebsiges Material Arch. Path.Anat. 1909:198:449 cited by Koiwai & Nahas (14).

18) Viti cited by Lissauer,M.: Beitrag zur Frage der experimentellen Endocarditis, Zentrabl. allg. Path. 1912:23:243 cited by Koiwai & Nahas (14).

19) Kinsella,R., Hayes,C.: Further study of the bacteremia of experimental streptococcus endocarditis. Proc. Soc. Exper. Biol. & Med. 1927:24:887.

20) Powers, J.H. Experimental production of mitral stenosis. Arch. Surg. 1929:18:1945.

21) Harken, D.: Experiments in intracardiac surgery: I. bacterial endocarditis. J. Thoracic. Surg. 1942:11 656.

22) Rabens,R.A., Geraci,J.E., Grindlay,S.H., Karlson,A.G. Edwards,J.E. Experimental bacterial endocarditis due to Streptococcus Mitis I: method of induction II: pathology of valvular and secondary lesions. Circulation 1955:11:199-205 - 206-214.

23) Walker,W.F., Hamburger,M.A., A study of experimental endocarditis in dogs, I: Production of the disease, its natural history and tissue bacteriology. J. Lab. Clin. Med. 1959,53,931-941.

24) Kinsella,R.A., Muether,R.D. Experimental streptococcal endocarditis. Arch. Int. Med. 1938:62:247-270.

25) Highman,B., Roshe,J., and Altland,P.D. Production of endocarditis and glomerulonephritis by single bacterial injections in dogs with aortic insufficiency. Fed. Proc. 1956, 15, No. 1684, 518-519.

26) Lillehei,C.W., Bobb,J., Visscher,M.D., Occurrance of endocarditis and valvular deformities in dogs with A.V. fistuls. Ann. Surg. 1950,132,577-590

27) Lillehei,C.W., Bobb,J., Visscher,M.D., Occurrance of endocarditis and valvular deformities in dogs with a-v fistulas. Pro. Soc. Exp. Biol. and Med. 1950,75,9-16.

28) Lee,S.H.B., Fisher,E.R., Little,A. A-v fistulae and bacterial endocarditis. Surgery 1962:52:463-467.

29) Angrist,A., Oka,M., Pathogenesis of bacterial endocarditis. J.A.M.A. Jan. 23, 1963:62:249-252.

30)Highman,B. and Altland,P.D. Effect of altitude and cobalt polycythemia, hypoxia, and cortisone on susceptibility of rats to endocarditis. Circulation Res. 1955:3:351-356.

31)Angrist,A., Oka,M., Nakao,K., Marquiss,J., Studies in experimental endocarditis: I. Production of valvular lesions by mechanisms not involving infection of sensitivity factors. Am. J. Path. 1960:36:181-191.

32) Nedzel,A.J. Experimental endocarditis. Arch. Path. 1937:24:143-200.

33) Miller,A.J., Pick,R.,Kline,J.K.,Katz,L.N. The susceptibility of dogs with chronic impairment of cardiac flow to staphylococcal valvular endocarditis. Circulation 1964:30:417-424.

34) McGeown,M. Bacterial endocarditis. Experimental study of healing. J. Path. and Bact. 1954:67:179-186.

35)MacNeal,W.J., Spence,M.J., Wasseen,M., Experimental production of endocarditis lent. Amer. J. Path. 1939:15:695-705.

36)Oka,M., Shirota,A., Angrist,A., Experimental endocarditis: endocrine factors in valve lesions on a-v shunt rats. Arch. Path. 1966:82:85-92.

37)Garrison,P.K. and Freedman,L.R. Experimental endocarditis I: Staphylococcal endocarditis in rabbits resulting from placement of a polyethylene catheter in the right side of the heart, Yale J. Biol. & Med. 1970:42:394-410.

38)Smits,H., and Freedman,L.R. Prolonged venous catherization as cause of sepsis. New Eng. J. Med. 1967:276:1299-1233.

39) Moran,J.M., Atwood,R.P., and Rowe,M.I. Clinical and bacteriologic study of infections associated with venous cutdowns. New Eng. J. Med. 1965:272: 554-560.

40)Collins,R.N., Braun,P.A., Zinner,S.H., and Kass,E.H. Risk of local and systemic infection with polyethylene intravenous catheters. New Eng. J. Med. 1968:279:340-343.

41) Jarcho,S. Historical Milestones: Experimental Endocarditis (Wyssokowitsch, 1886) Amer. J. Cardiol. 1969:24:876-879.

42) Cates,J.E., Christie,R.V. Subacute Bacterial Endocarditis. Quart. J. Med. 1951:20:93.

43) Middleton,W.S., Burke,M. Streptococcus viridans endocarditis lenta. Amer. J. Med. Sci. 1939:98:301

44) Schaub,F. Klinik der bakteriellen endocarditis (Berlin-Gottingen-Heidelberg, 1960) cited by Frank et al Bacterial endocarditis limited to the tricuspid valve. Germ. Med. Monthly 1968:13:120.

45) Horder,T.J. Infective endocarditis. Quart. J. Med. 1909:2:289.

46) Blumer,G. Subacute bacterial endocarditis Med. 1923:2:105.

47) Brauch, F. Verh. dtsch. Ges. Kreisl.-Forsch. 247:1954 cited by Frank et al. see (44).

48) Oka,M. Belenky,D., Brodie,S., & Angrist,A. Studies of bacterial susceptibility of heart valves. Lab. Invest. 1968:19:113.

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